Smoking and Other Risk Factors for Lung Cancer in Women [1,2]

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ABSTRACT—A case-control study among white women in Los Angeles County was conducted to investigate the role of smoking and other factors in the etiology of lung cancer in women. A total of 149 patients with adenocarcinoma (ADC) and 71 patients with squamous cell carcinoma (SCC) of the lung and their age- and sex-matched controls were interviewed. Personal cigarette smoking accounted for almost all of SCC and about half of ADC in this study population. Among nonsmokers, slightly elevated relative risk(s) (RR) for ADC were observed for passive smoke exposure from spouse(s) [RR=1.2; 95% confidence interval (CI)=0.5, 3.3] and at work (RR=1.3; 95% CI=0.5, 3.3). Childhood pneumonia (RR=2.7; 95% CI=1.1, 6.7) and childhood exposure to coal burning (RR=2.3; 95% CI=1.0, 5.5) were additional risk factors for ADC. For both ADC and SCC, increased risks were associated with decreased intake of β-carotene foods but not for total preformed vitamin A foods and vitamin supplements.—JNCI 1985; 74:747-751.

Lung cancer is now the fourth most common cancer in women (*1*) and has been projected to be the leading cause of cancer mortality among women by the mid-1980's (*2*). Causes of lung cancer, other than cigarette smoking (*3*), have not been clearly identified, but associations with exposure to passive smoking (*4-6*), exposure to combustion products of heating and cooking fuels (*7*), and occupational exposures (*8-10*) have been suggested. In addition, lung "scarring" (*11*) and a low dietary intake of β-carotene (*12-14*) and preformed vitamin A (*15-17*) may increase the risk of lung cancer.

This paper reports a case-control study of ADC and SCC of the lung in white females in Los Angeles County. Each of the above-mentioned factors was investigated.

METHODS

Female patients diagnosed with primary ADC or SCC of the lung were prospectively identified by the CSP, the population-based tumor registry for Los Angeles County (*18*), between April 1, 1981, and August 31, 1982. On the basis of information collected routinely by the CSP, we limited eligibility to white Los Angeles County residents, with no history of cancer (other than non-melanoma skin cancer) and under age 76 at diagnosis; we verified these variables at interview. We also excluded cases if they were born outside the United States, Canada, or Europe; were not English-speaking; or were not residents of Los Angeles County at the date of diagnosis.

A total of 490 eligible cases were identified. Of these patients, 190 had died or were too ill to participate by the time we contacted their attending physician. Permission was granted to contact 272 of the remaining 300 patients. Eight patients were not located, and 44 refused to be interviewed so that we obtained completed questionnaires on 220. On the basis of information on the CSP abstract, no significant differences were noted between those interviewed and those not interviewed in terms of age, marital status, religion, and smoking status recorded on medical records. However, those who were not interviewed were more likely to have distant metastases at the time of diagnosis (58%) compared to those who were interviewed (11%). Comparable percentages of eligible SCC (43%) and ADC (46%) patients were interviewed.

We selected one individually matched neighborhood control for each interviewed case. The control had to fulfill all the criteria given above for cases (with reference date taken to be the same as that of the matching case) and, in addition, was matched with the case on date of birth ($\pm$5 yr of birth date). Our control selection algorithm defined a specified sequence of houses to be visited in the neighborhood where the case lived at date of diagnosis. Our goal was to interview the first eligible resident in this sequence. If no one was home at the time of the visit, we left an explanatory letter and made a follow-up visit after several days. For any patient, 80 housing units were visited and 3 return visits were made before failure to secure a matched control was conceded. In 150 instances the first eligible person agreed to participate, in 55 instances the second eligible control in the sequence was interviewed, and in 15 instances the third eligible control was interviewed.

Cases and controls were interviewed on the telephone with the use of a structured questionnaire designed to elicit information on personal smoking habits, exposure to passive tobacco smoke, lung diseases, dietary intake of vitamin A, types of heating and cooking fuels ever used, and reproductive history. We also obtained a lifetime history of all jobs (job title, activities, and exposure) of at least 6 months' duration.

For childhood passive smoking exposure, we asked about the smoking habits (i.e., amount and years of smoking) of father, mother, or other household members

ABBREVIATIONS USED: ADC=adenocarcinoma; CI=confidence interval; CSP=University of Southern California/Los Angeles County Cancer Surveillance Program; RR=relative risk(s); SCC=squamous cell carcinoma.

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when they lived with the respondent during her childhood and teenage years. For passive smoke exposure during adult life, we asked about the smoking habits of spouse(s) and other household members when they lived with the respondent. Passive smoke exposure at work was assessed only in terms of the average number of hours per day to which the respondent believed she was exposed at each job.

The questions on vitamin A intake specifically asked about average frequencies of consumption of 21 vegetables and fruits that are high in β-carotene and 7 foods that contained preformed vitamin A during the calendar year 3 years before diagnosis of the case (*19*). Pattern of use of vitamin supplements was also assessed for the same period. On the basis of U.S. Department of Agriculture tables of food values for standard portion size (common household measure) of each item (*20*), we estimated average daily intake of β-carotene (or vitamin A) by summing the product of the β-carotene (or vitamin A) content of each food item and its reported frequency of consumption. Quartiles of consumption were constructed on the basis of the intake pattern of the 220 controls.

All cases were diagnosed microscopically. Their routine pathology reports were reviewed for mention of lung scarring.

Statistical analysis was conducted with the use of multivariate logistic regression methods for individually matched case-control studies (*21*). RR were estimated by odds ratios. A case-control pair was excluded from any given analysis if the information for either the case or the control was not known for the relevant variable(s). Since personal smoking will often, if not always, confound other associations, RR for other factors were always given after adjustment was made for personal smoking.

For ADC, RR for certain factors were given separately for nonsmokers, ex-smokers, and current smokers; this was not done for SCC because the numbers of nonsmokers and ex-smokers were too few.

RESULTS

We interviewed 149 ADC and 71 SCC cases and their matched controls. The mean age at diagnosis was 59.7 years for ADC cases and 61.4 years for SCC cases. The mean ages (at date of diagnosis of the index case) for the respective control groups were 59.5 and 61.1 years.

Personal cigarette smoking.—For both ADC and SCC, there was a significant trend in risk associated with increasing number of cigarettes smoked per day and with decreasing age at which smoking began (table 1). Both aspects of smoking remained significant after adjustment was made for the other.

Passive smoking.—Families tended to share similar smoking behavior. Controls whose father, mother, or spouse(s) smoked were more likely to smoke, to be heavy smokers, and to start at a younger age than controls whose family members did not smoke. For ADC and SCC, after adjustment was made for personal smoking habits, there were no significantly increased risks for having a mother, a father, or spouse(s) who smoked or for being exposed at work (table 2).

For nonsmoking ADC cases, we did not observe any elevated risk associated with passive smoke exposure from either parents (RR=0.6; 95% CI=0.2, 1.7), from spouse(s) (RR=1.2; 95% CI=0.5, 3.3), or at work (RR=1.3; 95% CI=0.5, 3.3). Increasing RR (RR=1.0, 1.2, 2.0) were found with increasing years (0, 1-30, ≥31) of passive smoke exposure during adult life from spouse(s) and at work, but the results were not statistically significant. Since the exposures may have occurred concurrently, the years of exposure represent units rather than chronologic time of exposure.

Childhood exposures.—For both ADC and SCC, no significant association was found with history of lung diseases (specifically, asthma, bronchitis, pneumonia, tuberculosis, fungal diseases, emphysema, and lung abscess) diagnosed by a physician at least 5 years before diagnosis of the case. When the analysis was restricted to lung diseases that occurred before age 16 (childhood), a significantly elevated RR for pneumonia was observed for ADC after adjustment was made for personal smoking habits (RR=2.7; 95% CI=1.1, 6.7), and the RR for SCC (RR=2.9; 95% CI=0.5, 17.4) was in the same direction. Parental smoking did not explain this effect. Table shows that for ADC, the effect of childhood pneumonia was most apparent among nonsmokers: Of the 2

TABLE 1.—*Personal smoking habits of cases and controls*

Smoking status	ADC			SCC		
	RR	95% CI	Case/control	RR	95% CI	Case/control
Nonsmoker	1.0		29/62	1.0		2/30
Ex-smoker[a]	1.2	0.6, 2.3	21/37	7.7	0.8, 70.3	8/18
Current smoker	4.1[b]	2.3, 7.5	99/50	35.3[b]	4.7, 267.3	61/23
Current smoker: No. cigarettes/day						
1-20	2.7	1.4, 5.4	38/28	17.7	2.3, 138.2	19/14
≥21	6.5[b]	3.1, 13.9	61/22	94.4[b]	9.9, 904.6	42/9
Current smoker: age started to smoke, yr						
≥25	1.1	0.4, 3.2	8/14	7.8	0.8, 73.7	6/5
19-24	2.5	1.0, 5.8	22/15	47.1	4.4, 498.5	18/7
≤18	8.0[b]	3.6, 17.9	69/21	115.7[b]	9.8, 1371.2	37/11

[a] Had stopped smoking at least 3 yr before diagnosis year of case.
[b] P (linear trend) <.001.

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TABLE 2.—*Exposure to passive smoking in cases and controls*

Smoking status	ADC		SCC	
	Adjusted RR[a]	95% CI	Adjusted RR[a]	95% CI
Mother smoked	1.7	0.8, 3.5	0.2	0.0, 1.5
Father smoked	1.3	0.7, 2.3	0.9	0.3, 2.9
Spouse(s) smoked[b]	1.2	0.6, 2.5	1.0	0.1, 7.6
Exposure at the workplace	1.2	0.8, 2.2	2.3	0.7, 7.9

[a] Adjusted for number of cigarettes smoked per day and age at starting to smoke.
[b] We eliminated from the analysis 15 pairs of ADC and 4 pairs of SCC in which either the case or the control was never married.

nonsmoking ADC cases, 8 (28%) gave a history of childhood pneumonia.

Elevated RR, adjusted for personal smoking habits, were observed for exposure to burning coal used for heating or cooking in a stove or fireplace during the majority of childhood and teenage years (ADC: RR=2.3; 95% CI=1.0, 5.5. SCC: RR=1.9; 95% CI=0.5, 6.5). For ADC, elevated RR were observed in each personal smoking habit category (table 3).

TABLE 3.—*RR and 95% confidence intervals of ADC of the lung according to childhood pneumonia and coal burning by personal smoking habits*

Exposure	RR (95% CI) among:		
	Nonsmoker	Ex-smoker	Current smoker
Childhood pneumonia[a]			
No	1.0	1.4 (0.6, 2.4)	5.1 (2.5, 10.3)
Yes	3.1 (1.0, 9.9)	1.5 (0.2, 10.8)	10.9 (2.1, 57.9)
Childhood coal burning[b]			
No	1.0	1.5 (0.6, 3.5)	6.3 (3.0, 13.3)
Yes	3.2 (0.9, 11.8)	4.3 (1.0, 17.8)	9.5 (2.1, 41.9)

[a] Before age 16. The analysis was based on 149 case-control pairs of ADC.
[b] Includes heating or cooking with coal burned in a stove or fireplace during childhood and teenage years. The analysis was based on 143 case-control pairs of ADC.

Dietary vitamin A.—Table 4 presents RR for ADC, adjusted for personal smoking habits, by quartiles of indices of vitamin A consumption. Because of the smaller sample size of SCC cases, the indices were dichotomized. For ADC, a significantly increased risk was observed only for those in the lowest quartile of β-carotene consumption (<2,000 IU/day) compared to those in the highest quartile (>4,000 IU/day), but no appreciably increased risks were observed for those in the intermediate groups. For SCC, an elevated, but not statistically significant, RR was observed for women with β-carotene intake below the median. When those in the lowest quartile of β-carotene consumption, i.e., less than 2,000 IU/day, were compared to those consuming more than 2,000 IU/day, the unadjusted RR was increased to 1.7 (from 1.5), but after adjustment the RR was not greater than comparisons above and below the median (both RR=1.5).

There was no association with an index of total preformed vitamin A (i.e., dairy products, eggs, liver, and vitamin supplements) for either cell type. However, for ADC and SCC, an association was observed for dairy products and eggs (table 4).

Other factors.—We could find no association between any occupation or occupational category and risk of ADC or SCC, but there was an excess number of cooks (4 cases and 2 controls) and beauticians (8 cases and 5 controls) among cases; both occupations have been suggested in previous studies. Elevated RR adjusted for personal

TABLE 4.—*Dietary intake of β-carotene, total preformed vitamin A, and dairy products and eggs among cases and controls*

Quartile	β-Carotene[a]		Total preformed vitamin A[b,c]		Dairy products and eggs[c]	
	Adjusted RR[d]	95% CI	Adjusted RR[d]	95% CI	Adjusted RR[d]	95% CI
			ADC			
1 (high)	1.0		1.0		1.0	
2	0.8	0.3, 2.0	0.6	0.3, 1.4	1.7	0.8, 3.9
3	1.3	0.6, 2.7	1.1	0.5, 2.5	2.2	1.0, 4.8
4	2.5	1.1, 5.7	1.2	0.5, 2.8	2.7	1.2, 5.8
			SCC			
1 and 2	1.0		1.0		1.0	
3 and 4	1.5	0.6, 3.8	1.0	0.4, 2.4	1.6	0.7, 3.9

[a] Includes 21 vegetables and fruits: leafy lettuce, other leafy green, broccoli, carrots, tomatoes, green peas, green beans, lima beans, asparagus, summer squash, winter squash, sweet potatoes and/or yams, green pepper, red pepper, hot red chili pepper, cantaloupe, watermelon, peaches, apricots, nectarines, and tomato and/or V8 juice. Analysis was based on 147 pairs of ADC and 69 pairs of SCC.
[b] Includes eggs, cheese, butter and/or margarine, cream, milk, beef and/or calf liver, chicken and/or turkey liver, and vitamin supplements.
[c] Analysis was based on 147 pairs of ADC and 71 pairs of SCC.
[d] Adjusted for number of cigarettes smoked per day.

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smoking habits were observed for a history of hysterectomy (RR=1.7; 95% CI=0.9, 3.2) and nulliparity (RR=1.7; 95% CI=0.8, 3.7) among ADC cases and a history of miscarriage (RR=1.5; 95% CI=0.5, 4.9) among SCC cases.

Multiple logistic regression analysis was conducted to assess the possible confounding effects of personal smoking habits, childhood pneumonia, childhood coal burning, and β-carotene intake. The results were similar to those when each factor was adjusted for personal smoking habits alone.

DISCUSSION

This case-control study examined risk factors for the two main cell types of lung cancer in women—ADC and SCC. Although histologic typing was done by the individual pathologist at each participating hospital, studies comparing interobserver and intraobserver variability in classification of lung cell types reported a high concordance rate for cell types other than large cell carcinoma, which was excluded in this study (*22, 23*).

In this study population, about half of ADC and almost all of SCC can be attributed to personal smoking habits; the amount smoked and the age at which smoking began were strong determinants of risk of disease. However, there are marked differences in the strength of association between smoking and cell type of lung cancer, as has been noted previously (*24, 25*).

The role of passive smoking in the etiology of ADC among nonsmokers is not clear. Our data are not consistent with the findings with regard to nonsmokers obtained by Hirayama (*4*) and Trichopoulos et al. (*5*) who reported a twofold to threefold increased risk due to passive smoking. However, the histology of the cases in these studies is not clear, and their data suggest that any effect of passive smoking is larger for SCC cases (*5, 6*). Of our 29 nonsmoking ADC cases, 12 were bronchoalveolar cell carcinomas, and this cell type is specifically mentioned by Correa et al. (*6*) to have a weaker association with passive smoking. The effect of passive smoking by cell type of lung cancer needs to be investigated further in studies with much larger numbers of nonsmokers.

Childhood lung disease may have a role in lung cancer etiology. Certain features of the lung of a child (e.g., susceptibility to airway closure and high peripheral resistance) might make it more vulnerable to residual abnormalities from respiratory illness (*26*). This notion is supported by observations that both smokers and nonsmokers with childhood respiratory diseases have impaired lung function capacity, that their rate of decline in ventilatory function capacity with age is more rapid than that in individuals without childhood respiratory problems, and that they have higher rates of clinical diagnosis of chronic obstructive pulmonary disease (*27, 28*). Women with childhood respiratory problems may have incurred epithelial damage to the airway resulting in airway hyperreactivity and are more susceptible to other insults to the lung. We cannot rule out the possibility of a chance finding or of preferential recall of childhood pneumonia by cases. However, our data appear to be internally consistent, since we found a significantly higher frequency of lung scarring mentioned in the pathology reports among cases with previous childhood pneumonia (12/30=40%) compared to those without (39/189=21%).

The association of lung cancer risk with exposure to coal heating or cooking warrants further investigation. Although coal was identified as the major heating or cooking fuel used during childhood and teenage years of a significantly higher proportion of cases, we did not have detailed information on the years of use. Excess risks of lung cancer have been reported for coke oven workers (*29, 30*) and British gas workers (*31*) who were heavily exposed to products of coal carbonization.

Studies of men suggest that their lung cancer risk is lowered by greater dietary β-carotene (*12-14, 32, 33*) and vitamin A intake (*15, 17, 32, 33*), but the evidence for women is less clear (*12, 13, 32, 33*). We observed a significantly increased risk for ADC with the lowest level of β-carotene consumption and a similar association for SCC. These results are consistent with findings for females in Singapore (*12*) and in Japan (*13*), but they are not supportive of data for females in Hawaii (*32*) and England (*33*). Our observation of no association with an index of total preformed vitamin A (i.e., dairy products, eggs, liver, and vitamin supplements) and no association with total vitamin A intake (preformed vitamin A and β-carotene—data not shown due to domination by preformed vitamin A) is consistent with findings for females in Hawaii (*32*). Conflicting findings have been reported for subgroups of preformed vitamin A foods and supplements. A higher consumption of liver and vitamin supplements has been reported previously for female cases as compared to controls, but the opposite results have been observed for males (*33, 34*). Our data show no case-control difference in the intake pattern of vitamin supplements and a higher consumption of liver among cases. Our finding of an elevated lung cancer risk associated with low levels of intake of dairy products has not been reported for females, although similar results have been observed for males (*15-17*). Our results on the role of β-carotene and preformed vitamin A were similar for ADC and SCC, despite suggestions that vitamin A (or β-carotene) is more strongly protective against SCC than against ADC (*17*).

Initial reports of an inverse relationship between blood retinol levels and subsequent risk of cancer at all sites (*35, 36*) have not been supported by recent studies (*37, 38*). This situation emphasizes the need to reexamine even the consistently observed association of vitamin A (or β-carotene) intake with male lung cancer.

Possible sources of bias in our data must be considered. Both lung cancer cases and controls were derived from population-based samples. However, because this disease is debilitating and rapidly fatal, 190 patients had died or were too ill to participate by the time of initial contact. We did not conduct proxy interviews because questions on childhood exposures and dietary history could not be assessed adequately. As expected, the group who was n

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interviewed was more likely to have metastatic disease at diagnosis but was similar in all demographic variables measured. In addition, information abstracted from medical records showed similar smoking status for those interviewed and those not interviewed. If cases who were not interviewed because of poor survival differed from those who survived longer and were interviewed in terms of the other risk factors under study, this could have biased our results. However, this appears unlikely since our data showed that histories of childhood pneumonia and exposure to coal fires were similar among cases regardless of stage of disease at diagnosis. There is also no evidence that cancer survival is associated with dietary vitamin A intake.

The etiology of SCC can be explained almost entirely by cigarette smoking. Cigarette smoking, however, explains only about half of the ADC cases. On the basis of this study, childhood lung disease and exposure to coal fires in childhood explain at least another 22% of ADC cases. Passive smoking and vitamin A may be involved, but more research is needed to clarify their roles in lung cancer etiology.

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